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## Neonatal seizures and therapeutic hypothermia for hypoxic-ischemic encephalopathy

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### Abstract

Neonatal seizures are associated with morbidity and mortality. Hypoxic-ischemic encephalopathy (HIE) is the most common cause of seizures in newborns. Neonatal animal models suggest that therapeutic hypothermia can reduce seizures and epileptiform activity in the setting of hypoxia-ischemia, however data from human studies have conflicting results. In this research highlight, we will discuss the findings of our recent study that demonstrated a decreased seizure burden in term newborns with moderate HIE treated with hypothermia.

### Keywords

newborn; hypoxic-ischemic encephalopathy; seizure; therapeutic hypothermia

Neonatal seizures occur in up to 4 per 1000 live births in the United States [1–3]. The most common etiology of seizures in neonates is hypoxic-ischemic encephalopathy (HIE) due to perinatal asphyxia [2]. Seizures are an important risk factor for abnormal neurodevelopment and epilepsy after HIE [4–6], and seizure burden in neonatal HIE is strongly related to brain injury detected by magnetic resonance imaging (MRI) [6,12,13]. There is increasing evidence from animal and human studies that seizures themselves may be harmful to the developing brain, and confer a risk for adverse outcomes independent of the severity of HI injury detected on MRI [14–18].

Therapeutic hypothermia is the only known effective and clinically available treatment for neonatal HIE [7–11]. Animal studies indicate that therapeutic hypothermia can reduce seizures and epileptiform activity in the setting of hypoxia-ischemia [19–21], however clinical data in human infants have been conflicting. Three observational studies showed a reduced incidence and severity of seizures among neonates with HIE who were treated with

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#### Conflict of Interest:

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therapeutic hypothermia [22–24]. Two studies showed a lower burden of electrographic seizures by continuous electroencephalogram (EEG) monitoring: (1) among neonates with moderate encephalopathy [22], and (2) after accounting for severity brain injury on MRI [23]. In addition, in a small cohort from our center, neonates who were treated with therapeutic hypothermia and found to have arterial ischemic stroke on MRI had a lower likelihood of seizure as compared to those neonates with stroke who were not cooled [24]. In contrast, meta-analyses of randomized controlled trials of therapeutic hypothermia for neonatal HIE have failed to show an association between therapeutic hypothermia and reduced seizure burden [8,9]. The potential anti-epileptogenic effects of therapeutic hypothermia have important clinical implications, since some seizure medications have limited effectiveness in newborns [25] and may be harmful [26].

We recently examined the relationship between therapeutic hypothermia and the cumulative incidence of seizures by examining a cohort of neonates with HIE who were admitted to our center either before or after the initiation of our cooling program [27]. Among 224 newborns included in our study, 151 were treated with hypothermia. Seizure monitoring in the subjects born prior to onset of the cooling program was at the discretion of the treating physician, whereas cooled newborns had continuous monitoring with amplitude-integrated EEG and conventional video EEG from admission until the completion of rewarming after therapeutic hypothermia. Cooled newborns with moderate encephalopathy were much less likely to have either clinical or electrographic seizures compared to non-cooled newborns (cooled: 26% vs. non-cooled: 61%,  $P < 0.001$ ), but there was no difference in the risk of seizures among newborns with severe encephalopathy (cooled: 87% vs. non-cooled: 83%,  $P = 0.8$ ). Since continuous EEG monitoring was implemented alongside hypothermia at our center, it is likely that EEG seizure frequency was under-estimated in the non-cooled group when monitoring was more limited and at the discretion of the treating physician, however this would lead to an under-estimate of the magnitude of reduced seizure burden associated with hypothermia and consequently does not change the interpretation of the results. Our data support preclinical and clinical studies that suggest therapeutic hypothermia may have anti-epileptogenic effects. Studies are underway to evaluate the relationship between seizure burden and neurodevelopmental outcome in this cohort.

Our results are consistent with clinical trial data that indicate that newborns with moderate encephalopathy benefit most from therapeutic hypothermia [28]. Further studies are needed to uncover the mechanisms that underlie the reduced risk of seizures associated with therapeutic hypothermia in newborns with moderate HIE, as well as the potential anti-epileptogenic role for hypothermia in other clinical settings.

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